RESEARCH ARTICLE

World Health Organization estimates of the global and regional disease burden of four foodborne chemical toxins, 2010: a data synthesis [version 1; referees: 2 approved, 1 approved with reservations]

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Abstract

Background

Chemical exposures have been associated with a variety of health effects; however, little is known about the global disease burden from foodborne chemicals. Food can be a major pathway for the general population's exposure to chemicals, and for some chemicals, it accounts for almost 100% of exposure.

Methods and Findings

Groups of foodborne chemicals, both natural and anthropogenic, were evaluated for their ability to contribute to the burden of disease. The results of the analyses on four chemicals are presented here - cyanide in cassava,

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peanut allergen, aflatoxin, and dioxin. Systematic reviews of the literature were conducted to develop age- and sex-specific disease incidence and mortality estimates due to these chemicals. From these estimates, the numbers of cases, deaths and disability adjusted life years (DALYs) were calculated. For these four chemicals combined, the total number of illnesses, deaths, and DALYs in 2010 is estimated to be 339,000 (95% uncertainty interval [UI]: 186,000-1,239,000); 20,000 (95% UI: 8,000-52,000); and 1,012,000 (95% UI: 562,000-2,822,000), respectively. Both cyanide in cassava and aflatoxin are associated with diseases with high case-fatality ratios. Virtually all human exposure to these four chemicals is through the food supply.

Conclusion

Chemicals in the food supply, as evidenced by the results for only four chemicals, can have a significant impact on the global burden of disease. The case-fatality rates for these four chemicals range from low (e.g., peanut allergen) to extremely high (aflatoxin and liver cancer). The effects associated with these four chemicals are neurologic (cyanide in cassava), cancer (aflatoxin), allergic response (peanut allergen), endocrine (dioxin), and reproductive (dioxin).

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Introduction

Chemicals in food are a worldwide health concern[1]. Foodborne chemicals, both natural and anthropogenic, have been a source of concern with respect to international trade[2–8], and various articles in the scientific literature have reported the health risks of chemical food contaminants[9–11]. The Dutch National Institute for Public Health and the Environment (RIVM) found that chemicals in food contributed as much as infectious agents to the foodborne burden of disease in the Netherlands[12].

In September 2006 the World Health Organization (WHO) organized a consultation to develop a strategy to estimate the global burden of foodborne disease[13]. The first meeting of the WHO Foodborne Disease Burden Epidemiology Reference Group (FERG), convened in September 2007[14], was the first of several meetings[15–17]. The FERG includes three hazard-based task forces: Enteric Disease Task Force, Parasitic Disease Task Force, and the Chemical and Toxins Disease Task Force (CTTF). A Country Studies Task Force, a Source Attribution Task Force, and a Computational Task Force were subsequently added to FERG. In the current study, the CTTF reports the estimates of the burden of disease of four chemicals.

Methods

At its first meeting, the CTTF identified groups of chemicals and toxins that are of highest priority in estimating the burden of foodborne disease. These included:

Elemental contaminants (e.g., lead, mercury, cadmium, manganese, arsenic)

Mycotoxins (e.g., aflatoxins, ochratoxins, fumonisins, trichothocenes)

Food additives (e.g., sulphites, nitrites/nitrates, benzoic acid)

Pesticides/residues (e.g., organophosphates, carbamates, DDT, pyrethrins)

Organic industrial pollutants (e.g., persistent organic pollutants)

Veterinary drugs/residues (e.g., antibiotics, hormones – but not antimicrobial residues)

Seafood toxins (e.g., tetrodotoxin, ciguatera, shellfish toxins, DSPs, PSPs, histamines)

Process contaminants (e.g., acrylamide, PAHs, choropropanol)

Allergens (e.g., peanuts)

Natural toxicants (e.g., cyanide in cassava, aminoglycosides)

Radionuclides and depleted uranium

The hazards were ranked on (1) the severity of potential health effects, (2) the prevalence of exposure, and (3) the availability of data to make burden estimates. After considerable discussion, the final list of chemicals/toxins for which the CTTF believed that burdens could be estimated were aflatoxin, cyanide in cassava, peanut allergen, dioxin and dioxin-like compounds, methylmercury, lead, arsenic, and cadmium. Only the results for aflatoxin, cyanide in cassava, peanut allergen, and dioxin are presented here. The results for the metals will be provided in a subsequent publication.

For each of the four chemicals, a systematic literature review was conducted. It was concluded that burden estimates could be developed for (1) cyanide in cassava and *konzo*; (2) peanut allergy; (3) aflatoxin and hepatocellular carcinoma (HCC); and (4) dioxin and hypothyroidism; and (5) dioxin and decrease in sperm count. The methodology employed for each is described below. Additional information may be found in the Supplementary material.

The metrics used to express burden are those of the WHO[19]. DALYs are the sum of years lived with disability (YLD) and years of life lost (YLL)[18]. YLD are estimated from the number of incident cases multiplied by the disability weight (DW) assigned to the disease and the duration of the disease from onset until remission or death[18]. YLL are estimated from the number of deaths, the distribution of age at death, and life expectancy[18]. The life expectancy used for the calculations is the projected life expectancy for the year 2050. Estimates of the number of incident cases were produced using United Nations country-level population data for 2010 using the 2012 Revision of World Population Prospects. Uncertainty around input parameters was estimated using Monte Carlo simulations; 10,000 samples from each input parameter were used to calculate 10,000 estimates of cases, deaths or DALYs. The 2.5th and 97.5th percentile of each set of the 10,000 estimates yielded a 95% uncertainty interval (UI) which is presented around the median[19]. Detailed information on the input parameters used in the DALY calculations for the different hazards is provided in the Supplementary material.

Cyanide in cassava

Cassava is an important staple for over 800 million people in approximately 80 countries, mostly in sub-Saharan Africa but also in Asia, the Pacific, and South America[20]. Cassava tubers contain a varying quantity of cyanogenic glucosides which protect the root against attack by animals and insects. Appropriate processing before consumption can reduce cyanogenic glucoside content of cassava. When high cyanogenic cassava is not processed correctly, high dietary cyanide exposure occurs. This often happens during times of famine and war. Cyanide in cassava is associated with acute cyanide poisoning and several diseases including *konzo*[21]. Worldwide reports exist of acute poisoning from cyanide in cassava[21] exist, but the data are inadequate to make burden estimates. The data are sufficient, however, to make burden estimates of *konzo*. *Konzo* is an irreversible spastic paraparesis of sudden onset, associated with the consumption of bitter cassava[22,23] and a low protein intake[24]. It is a disease of extreme poverty. *Konzo* mostly occurs in epidemics, but sporadic cases are also reported. The case definition includes the following criteria: (1) a visible symmetrically spastic abnormality of gait while walking and/or running; (2) a history of abrupt onset (less than one week), followed by a non-progressive course in a formerly healthy person; (3) bilaterally exaggerated knee and/or ankle jerks without signs of disease in the spine[24,25].

Because *konzo* mostly affects remote rural areas where health infrastructure is poor or non-existent, many cases remain undiagnosed or unreported, so the true burden of disease remains unknown. No

cases have been reported from urban areas. A total of 2376 *konzo* cases have been reported in 5 countries in Africa (Cameroon, Central African Republic, Democratic Republic of Congo [DRC], Mozambique, and United Republic of Tanzania)[21], corresponding to 149 cases per year for 122 million people. Dividing the average annual number of cases for each country by the corresponding country population produces an observed incidence ranging from 0.043 to 0.179 per 100,000. The degree of underestimation is difficult to determine as *konzo* occurs in rural areas, often under conditions of war, and the disease is not notifiable. The only reported calculation of underestimation was that of Tylleskar[25] in the DRC in 1994, when he estimated that at least twice as many cases may have occurred as those reported. The underestimation in the DRC is likely to be much greater more recently, due to war and displacement. It was therefore decided to account for the uncertainty in the underreporting by applying an expansion factor ranging uniformly from 1 to 10 to the observed cases. The mean annual incidence rate was therefore estimated as 0.9/100,000 (0.04 to 1.8/100,000). Our estimate of the burden of *konzo* is restricted to the 5 African countries described above and Angola. The decision to include Angola is based on a report to the World Congress on Neurology suggesting that cases have occurred in that country[26]. Although cassava consumption occurs in tropical areas throughout the world, the term *konzo* has only been used to describe cases in Africa. The incidence of *konzo* in other countries in Africa and other parts of the world is assumed to be zero.

We assumed the age of onset and gender distribution of these cases to be that observed by Tylleskar[25]. The *konzo* case-fatality ratio is approximately 21% based on four studies[25,27–29]. The age and gender distribution of fatal cases was assumed to be that of Tshala-Katumbay[27].

The onset of paraparesis in *konzo* is abrupt, usually within minutes or hours, with occasional progression during the first days of the illness. After that time, the paraparesis is non-progressive and permanent. As a result, duration is defined as lifelong for non-fatal cases. For fatal cases, it was assumed that death occurred one to seven years after onset, with a most likely value of three years after onset, following Banea *et al.*[28] and Tylleskar *et al.*[30].

There is no DW specifically for *konzo*. The WHO defined three severity levels for *konzo*: (1) Mild = able to walk without support; (2) Moderate = uses one or two sticks or crutches to walk; and (3) Severe = not able to walk[24]. The Global Burden of Disease (GBD) 2010 DWs for mild, moderate, and severe motor impairment are 0.012, 0.076, and 0.377, respectively[31]. The distribution of *konzo* severity among 753 patients from nine different studies were mild (63%), moderate (27%) and severe (10%)[27,28,30,32–37]. This distribution and the disability weights described above were used to assign a disability weight of 0.065 to *konzo*.

Peanut allergen

Prevalence data on peanut allergy were used to make estimates of incidence since allergy occurs early in life (< 5years) and is believed to be lifelong[38–42]. All peanut allergy cases are assumed to be the result of eating peanuts or peanut products. In western countries, the prevalence of clinical peanut allergy in children is 0 to 1.8% of the population[38], corresponding to incidence rates of 0 to 22.6 per 100,000. Limited data exist on the mortality rate of peanut-induced anaphylaxis, but the majority of studies found similar rates, ranging from 0 to 0.006 deaths per 100,000 person-years[38]. Incidence was estimated only for the WHO A level (high income) subregions; too few data exist to make estimates for other subregions[38]. Several studies have reported that 63–66% of cases are male[38], but given the uncertainty in this number, the gender distribution was assumed to be equal for the burden of disease calculations. No DW exists for peanut allergy. Mullins *et al.*[39] reported that 52% of cases referred to a specialist allergy medical practice in Australia suffered from mild symptoms (skin and subcutaneous tissue involvement only), 42% from moderate symptoms (features suggestive of respiratory, cardiovascular or gastrointestinal involvement), and 6% from severe symptoms (cyanosis, hypotension, confusion, collapse, loss of consciousness, incontinence). We propose the DW for peanut allergy be a weighted average accounting for this severity distribution. GBD 2010 DWs[31] for the health states defined in the category "Asthma: controlled" (DW=0.009) are considered applicable for mild and moderate cases (94%), and "Generic uncomplicated disease: anxiety about the diagnosis" (DW=0.054) for severe cases (6%), because anxiety is known to impact quality of life in food allergic patients[43], leading to a severity-weighted DW of 0.012 for clinically relevant peanut allergy. Unlike other childhood allergies such as cow's milk and egg allergy, peanut allergy rarely resolves[44,45].

Aflatoxin

Aflatoxins are secondary metabolites of the fungi *Aspergillus flavus* and *A. parasiticus*, and less frequently other *Aspergillus* species such as *A. nomius*[46]. These species can be found in maize, peanuts (groundnuts), oilseeds, and tree nuts in tropical and subtropical regions[46]. It is believed that all aflatoxin exposure results from food consumption. We assumed a multiplicative model for the effects of aflatoxin exposure and hepatitis B virus (HBV) infection and estimated excess risk due to aflatoxin exposure as described by Liu and Wu[46]. To account for differences in background rates between the study population from which the cancer potency factor was derived[47] and global populations, we estimated population attributable fractions (PAFs) by country, and applied them to HCC incidence and mortality based on[48,49]. A Bayesian log-normal random effects model[50] was used to extrapolate available PAFs to countries without data. Age-specific incidence estimates were derived from a study in China comparing age-specific incidence of HCC in Qidong, a city in China with high aflatoxin exposure, and Beijing, a city with low aflatoxin exposure[51]. The YLD and YLL envelopes for HCC that are available from WHO were multiplied by the proportion of the burden due to aflatoxin. Thus no DW was directly involved in the calculation.

Dioxin

Dioxins are mainly byproducts of industrial processes, but can also result from natural phenomena such as volcanic eruptions and forest fires. More than 90% of human exposure to dioxins is through the food supply. The foods most often associated with dioxin contamination are meat, dairy products, fish, and shellfish[52]. Due to the bioaccumulation and lipophilic characteristics of dioxins, daily dietary exposure leads to accumulation of these compounds in human body fat. In adults this accumulation is thought to reach

a constant level (i.e., a steady state). Consequently, the dioxin body burden, rather than the daily exposure, is taken as the dose metric for chronic toxicity risk and the assessment of dioxins[53–58]. In this context the dioxin concentration in breast milk fat directly reflects the concentration in body fat[58–61].

Many national authorities have programs in place to monitor dioxin in the food supply and breast milk[61–63]. Dioxin-induced prenatal and postnatal hypothyroidism and prenatally induced reduced sperm production have been found to be the most sensitive non-cancer toxic endpoints for dioxins. Estimates for dioxin-induced prenatal and postnatal hypothyroidism and reduced fertility due to disturbed sperm formation were based on an exposure assessment, toxicity assessment, and the comparison of both assessments[64,65]. The exposure assessment is based on breast milk concentrations of dioxin from 50 countries[63]. The toxicity assessment utilizes the benchmark dose (BMD) approach[66–68] in which the dose response of postnatal total thyroxine (TT; decrease of TT4 in adult blood), prenatal thyroid stimulating hormone (TSH; increase in TSH in neonatal blood), and sperm production (reduced concentration of sperm cells) is analyzed. The toxicity and exposure assessments are compared to derive the transgression of a dioxin induced decrease in TT4, decrease in sperm cell count and increase in TSH across a physiological threshold indicating a disease status (i.e., incidence of hypothyroidism or impaired fertility). Additional details of these assessments may be found in Zeilmaker *et al.*[69]. The BMD analysis was performed on studies which served as the starting point for the derivation of a tolerable weekly intake (TWI)[54–57] or reference dose for dioxin (RfD)[58].

In a study of a mother-child cohort, Baccarelli *et al.* determined the relationship between maternal plasma dioxin concentration and TSH level[70]. A BMD analysis of these data resulted in a population distribution of the maternal body burden of dioxin corresponding to an increased TSH level of 5 µU/mL in offspring, a level not to be exceeded in 3% of newborns in iodine-replete populations[71].

Following administration of an acute oral dose to pregnant Long Evans rats on day 15 of gestation, Gray *et al.* measured the reduction in cauda epididymis sperm count in male offspring[72]. The resulting dose response data were used to calculate a BMD lower confidence limit (BMDL) and upper confidence limit (BMDU) dioxin body burden for various levels of reduction in sperm count. A WHO reference cut-off value for impaired fertility of 20×10^6 sperm cells/mL was used to link toxicity (sperm count reduction) to a disease status (impaired fertility) (i.e., the calculation of the probability of a male being born with dioxin-impaired fertility)[73].

A BMD analysis of a National Toxicology Program (NTP) two year feeding study in rats was used to make estimates of dioxin-induced thyroid toxicity. The NTP study administered 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)[74] and 2,3,4,7,8-pentachlorodibenzofuran[75] for periods of 14, 31, and 53 weeks. The concentrations were converted to toxic equivalent quotients[76] to enable a combined analysis of both congeners. BMDL and BMDU body burdens for reduction in TT4 were calculated for each of the exposure periods. A distribution of TT4 in human blood has been reported by Aoki *et al.*[71]. The 5th percentile of this distribution (65 nmol/L) was used as the cut-off for overt clinical hypothyroidism in adults.

The results of the BMD analyses and the breast milk concentrations for 50 countries were compared, taking account of possible differences between experimental animals and humans and among individual humans[64,65]. This comparison provided country-specific estimates of the incidence of dioxin induced prenatal and postnatal hypothyroidism and impaired fertility. The estimates were extrapolated to other countries for which no breast milk concentrations were available by means of Bayesian random effects modeling[50].

Results

Dataset 1. Raw data for Gibb *et al.* 2015, 'World Health Organization estimates of the global and regional disease burden of four foodborne chemical toxins, 2010'

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A detailed description of the data can be found in the text file provided ('Raw data legends').

The analyses presented here show that four selected chemicals already have a substantial impact on the foodborne burden of disease, particularly in low- and middle-income countries. Just these four agents are estimated to be associated with 339,000 illnesses (95% UI: 186,000–1,239,000); 20,000 deaths (95% UI: 8,000–52,000); and 1,012,000 DALYs (95% UI: 562,000–2,822,000), respectively, in the year 2010. These should be considered the "tip of the iceberg" in terms of foodborne chemicals and their impact on the global burden of disease. For peanut allergens, we were unable to estimate a burden for low- and middle-income countries due to data gaps. We also had to use an approximate disability weight, as there are data only on quality of life of patients with food allergy[38] and no specific data are available for peanut allergy.

The estimated number of incident cases, deaths, and DALYs of each of the diseases associated with chemicals is given in Table 1. The chemical associated with the most number of illnesses is dioxin; however, no deaths have been reported from the presence of dioxin in the food supply. The chemical associated with the greatest number of DALYs is aflatoxin. The DALY estimates for aflatoxin and dioxin have the least uncertainty; more uncertainty is associated with the DALY estimates for peanut allergen and cyanide in cassava. The annual incidence, mortality, and DALY rate of each chemical-associated disease per 100,000 population for each of the WHO regions is reported in Table 2. Peanut allergy is not reported in Table 2 because burden was estimated only for Americas Region A (AMR A) - United States, Canada, and Cuba); Europe A (EUR A) - primarily countries in western Europe; and Western Pacific Region A (WPR A) - Australia, Brunei Darussalam, Japan, and New Zealand. Burden estimates for cyanide in cassava are provided only for the African region (AFR) and assumed to be zero for other regions.

Table 1. Median number of foodborne illnesses, deaths, and DALYs, with 95% UIs, 2010.

CHEMICAL	FOODBORNE ILLNESSES (95% UI)	FOODBORNE DEATHS (95% UI)	FOODBORNE DALYS (95% UI)
Aflatoxin	21,757 (8,967–56,776)	19,455 (7,954–51,324)	636,869 (267,142–1,617,081)
Cyanide in cassava	1,066 (105–3,016)	227 (22–669)	18,203 (1,769–53,170)
Dioxin	193,447 (155,963–1,085,675	0 (0–0)	240,056 (192,608–1,399,562)
Peanut allergens*	107,167 (6,262–210,093)	28 (2–56)	99,717 (5,827–195,489)
TOTAL	338,611 (185,705–1,238,725	19,736 (8,210–51,700)	1,012,362 (562,087–2,822,481)

*Only the burden for AMR A, EUR A, and WPR A was assessed.

Table 2. Median rate per 100,000 foodborne illnesses, deaths, and DALYs by WHO region, with 95% UIs.

REGION		CHEMICAL			
		Aflatoxin	Cyanide in Cassava	Dioxin	Total
AFRO	FB Illnesses (95% CI)	0.4 (0.1–1)	0.1 (0.01–0.4)	0.2 (0.07–7)	0.7 (0.3–8)
	FB Deaths (95% CI)	0.4 (0.1–1)	0.03 (0.003–0.08)	0 (0–0)	0.4 (0.1–1)
	FB DALYs (95% CI)	15 (5–40)	2 (0.2–6)	0.2 (0.07–8)	18 (7–49)
AMRO	FB Illnesses (95% CI)	0.08 (0.02–0.6)	0 (0–0)	0.2 (0.05–6)	0.2 (0.1–7)
	FB Deaths (95% CI)	0.08 (0.02–0.6)	0 (0–0)	0 (0–0)	0.08 (0.02–0.6)
	FB DALYs (95% CI)	2 (0.4–15)	0 (0–0)	0.2 (0.07–9)	2 (0.6–24)
EMRO	FB Illnesses (95% CI)	0.2 (0.04–0.5)	0 (0–0)	2 (1–35)	2 (1–35)
	FB Deaths (95% CI)	0.1 (0.04–0.4)	0 (0–0)	0 (0–0)	0.1 (0.04–0.4)
	FB DALYs (95% CI)	4 (1–13)	0 (0–0)	2 (2–43)	7 (3–51)
EURO	FB Illnesses (95% CI)	0.02 (0.01–0.03)	0 (0–0)	1 (0.7–13)	1 (0.7–13)
	FB Deaths (95% CI)	0.02 (0.01–0.03)	0 (0–0)	0 (0–0)	0.02 (0.01–0.03)
	FB DALYs (95% CI)	0.5 (0.3–0.8)	0 (0–0)	1 (0.9–19)	2 (1–19)
SEARO	FB Illnesses (95% CI)	0.2 (0.08–0.6)	0 (0–0)	9 (8–32)	10 (8–32)
	FB Deaths (95% CI)	0.2 (0.08–0.5)	0 (0–0)	0 (0–0)	0.2 (0.07–0.5)
	FB DALYs (95% CI)	7 (2–17)	0 (0–0)	12 (10–41)	19 (13–54)
WPRO	FB Illnesses (95% CI)	0.6 (0.1–2)	0 (0–0)	0.05 (0.005–4)	0.8 (0.1–5)
	FB Deaths (95% CI)	0.5 (0.09–2)	0 (0–0)	0 (0–0)	0.5 (0.09–2)
	FB DALYs (95% CI)	16 (3–63)	0 (0–0)	0.07 (0.007–6)	16 (3–65)
GLOBAL	FB Illnesses (95% CI)	0.3 (0.1–0.8)	0.02 (0.002–0.04)	3 (2–16)	3 (3–17)
	FB Deaths (95% CI)	0.3 (0.1–0.7)	0.003 (0–0.01)	0 (0–0)	0.3 (0.1–0.8)
	FB DALYs (95% CI)	9 (4–24)	0.3 (0.03–0.8)	3 (3–20)	13 (7–39)

Figure 1 provides the DALYs per 100,000 inhabitants by global region. The regions with the highest burden per 100,000 inhabitants are the Southeast Asia Region (SEAR), Western Pacific Region (WPR), and the African Region (AFR). The AMR, Eastern Mediterranean Region (EMR), and EUR have the lowest DALYs per 100,000. Aflatoxin is the largest contributor to the burden in AFR and WPR. Dioxin makes the largest contribution in SEAR. Figure 2 contrasts the proportion of DALYs due to YLL and YLD for each of the four chemicals. Virtually all of the DALYs for aflatoxin and most of the DALYs for cyanide in cassava are due to YLL, whereas most of the DALYs for peanut allergen and all of the DALYs for dioxin are due to YLD. Figure 3 shows the uncertainty around the DALY estimates for each of the four chemicals. The chemical with the least uncertainty and the most number of DALYs is aflatoxin.

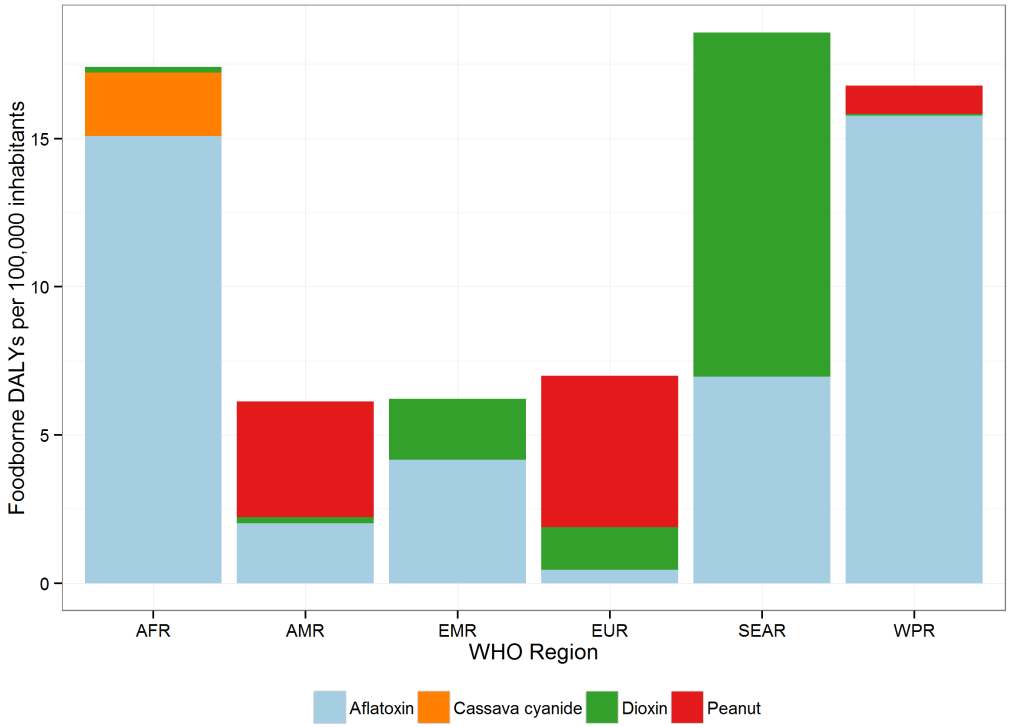

Figure 1. The relative contribution to the DALY incidence by each of four chemicals for each of the WHO regions.

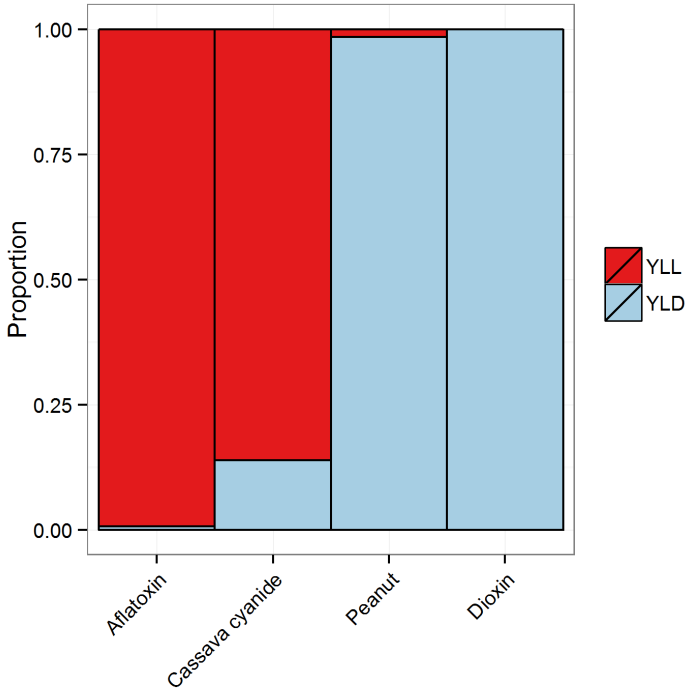

Figure 2. The relative contributions from YLLs and YLDs for each of four chemicals.

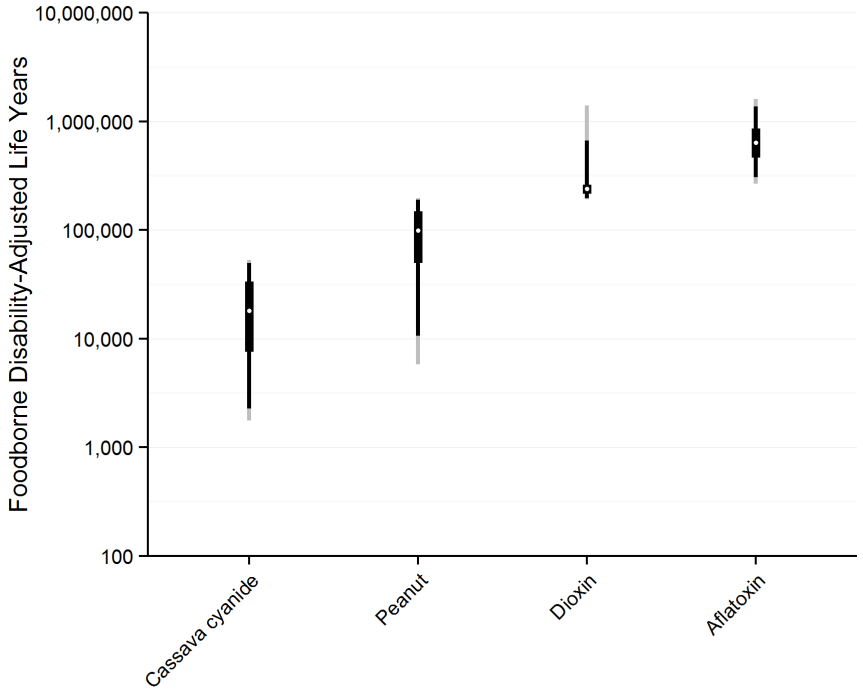

Figure 3. DALY for each of four chemicals from contaminated food ranked from lowest to highest with 95% UI (The dot in the middle of each box represents the median, the box the 50% UI, the dark bar the 95% UI, and the light bar the 95% UI).

Discussion

The assessment of burden of disease from chemicals in the food is a challenge on several levels. There are thousands of chemicals in production and many naturally occurring toxins. How many of these chemicals and toxins make it into the food supply is unknown. The health effects of chemicals may not be observed for years following exposure (e.g., aflatoxin and liver cancer, lead and cardiovascular disease). Longitudinal studies of these effects are expensive and time-consuming. Sufficient information is available, however, to make estimates of the burden for arsenic, cadmium, methyl mercury, and lead and possibly for other chemicals and toxins (e.g., fish toxins, aristolochic acid). Other chemicals (e.g., persistent organic pollutants) may not require elaborate epidemiological studies because the burden can be derived from biomonitoring data in combination with relevant toxicity data. Estimates of the burden for these chemicals will provide a much more comprehensive understanding of the impact that chemicals in the food supply have on the burden of disease.

As the relevant disease endpoints due to foodborne chemicals may arise from different causes, various approaches are possible for estimating incidence and mortality. A "top-down" approach uses an existing estimate of morbidity or mortality of the disease endpoint by all causes ("envelope") as a starting point. A population attributable fraction is then calculated for the hazard under consideration, and applied to the envelope to estimate the hazard-specific incidence. This method, which is the standard in global burden of disease estimations, was used for aflatoxin. A "bottom-up" or dose response approach uses dose-response and exposure information. The approach begins with selection of the appropriate dose response relationship between the chemical and the particular disease. This dose response relationship is then combined with the distribution of exposure within a population to derive an estimate of the incidence of the disease that is attributable to the exposure. A probabilistic version of this method, which is applied in chemical risk assessment, was used for dioxin[64,65]. The two approaches would result in the same results if perfect data were available, and if it can be assumed that the risk of exposure to a chemical is additive to the background risk from other causes. In reality, the available data for both approaches are limited and there is insufficient information to decide conclusively whether risks are additive, multiplicative or otherwise. This may result in considerable discrepancies between results from these methods. In this study, we chose a "top-down" approach for aflatoxin because the cancer potency factor derived by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[47] was based on a multiplicative model, and there is evidence for a high background rate in the study population underlying this estimate and the global population (see Supplementary material). Using the population attributable fraction approach, we estimated there were approximately 22,000 (95% UI 9,000–57,000) cases of aflatoxin-related HCC in 2010. A dose response approach[46] estimated that annually, 25,200–155,000 cases of HCC may be attributable to aflatoxin exposure. Even though the uncertainty intervals overlap, there is significant difference between these two approaches. There is evidence for a high background rate in the study population underlying this estimate and the global population (see Supplementary material), which may result in overestimation of mortality by the dose response approach. On the other hand, the

global liver cancer envelope may be underestimated, particularly in Africa[77,78], leading to underestimation of the aflatoxin attributable incidence.

It is hoped that the presentation here will raise awareness among countries planning their own foodborne burden of disease assessments to consider natural and anthropogenic chemicals. It is also hoped that this publication will lead to the development of chemical specific biomonitoring data to assess exposure and of epidemiologic data on other diseases associated with chemicals in food.

Data availability

F1000Research: Dataset 1. Raw data for Gibb *et al.* 2015, 'World Health Organization estimates of the global and regional disease burden of four foodborne chemical toxins, 2010', 10.5256/f1000research.7340.d107254[79]

Author contributions

Conceived and designed the experiments: HG, PMB, FW, JE, JC, MZ, PV, JIP, JB, GA, RA, YL, BB, HL, ML, AH, DB, EB.

Performed the experiments: FW, JE, JC, MZ, YL, BB, HL, MM, EB.

Analyzed the data: BD, FW, JE, JC, MZ, YL, BB, HL, MM, EB.

Wrote the first draft of the manuscript: HG.

Contributed to the writing of the manuscript: HG, AH, BD, DB, PMB, MZ, BB, JP, JB.

ICMJE criteria for authorship read and met: HG, BD, PMB, FW, JE, JC, MZ, PV, JIP, JB, GA, RA, YL, BB, HL, ML, AH, DB, EB.

Agree with manuscript results and conclusions: HG, BD, PMB, FW, JE, JC, MZ, PV, JIP, JB, GA, RA, YL, BB, HL, ML, AH, DB, EB.

Competing interests

HJG, BD, MPB, AHH, JB, PV, JIP, GA, RA, and DCB serve as members of the World Health Organization advisory body—the Foodborne Disease Burden Epidemiology Reference Group - without remuneration. The authors declare no competing interests.

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Supplementary material

Incidence, clinical outcomes, duration, disability weights, mortality, age and sex distribution of 4 chemicals/toxins transmitted through food.

Click here to access the data.

References

1. World health organization: **Food Safety: Chemical Risks**.
Reference Source
2. Derbyshire D: **Poisoned food in shops for THREE WEEKS: Supermarkets clear shelves of cakes and quiches containing contaminated eggs from Germany**.
Reference Source
3. Food and Agriculture Organization of the United Nations-Food Safety and Quality: **Melamine.**
Reference Source
4. Foodsafetynewscom: **Dioxin Scare Halts German Egg Sales**.
Reference Source
5. Kennedy J, Delaney L, McGloin A, *et al.*: **Public perceptions of the dioxin crisis in Irish pork**. University College Dublin. Geary Institute. 2009.
Reference Source
6. The Telegraph: **Germans Told to Avoid Eggs after Dioxin Contamination**.
Reference Source
7. World health organization: **Emergencies preparedness, response: Questions and Answers on melamine**.
Reference Source
8. NSW: **Follow up survey of cyanogenic glycosides in ready-to-eat cassava chips**. *New South Wales Food Authority*. 2012.
Reference Source
9. Gleason K, Shine JP, Shobnam N, *et al.*: **Contaminated turmeric is a potential**

source of lead exposure for children in rural Bangladesh. *J Environ Public Health.* 2014; **2014**: 1–5.
PubMed Abstract | Publisher Full Text | Free Full Text

10. Naujokas MF, Anderson B, Ahsan H, *et al.*: **The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem.** *Environ Health Perspect.* 2013; **121**(3): 295–302.
PubMed Abstract | Publisher Full Text | Free Full Text

11. Melkonian S, Argos M, Hall MN, *et al.*: **Urinary and dietary analysis of 18,470 Bangladeshis reveal a correlation of rice consumption with arsenic exposure and toxicity.** *PLoS One.* 2013; **8**(11): e80691.
PubMed Abstract | Publisher Full Text | Free Full Text

12. Van Kreijl CF, Knaap A, Van Raaij JMA: **Our food, our health- Healthy diet and safe food in the Netherlands**. *RIVM.* 2006.
Reference Source

13. WHO: **WHO Consultation to develop a strategy to estimate the global burden of foodborne diseases. Taking stock and charting the way forward**. 2006.
Reference Source

14. WHO: **WHO initiative to estimate the global burden of foodborne diseases. First formal meeting of the foodborne disease burden epidemiology reference group (FERG). Implementing strategy, setting priorities and assigning tasks**. 2007.
Reference Source

15. WHO: **WHO initiative to estimate the global burden of foodborne diseases. Second formal meeting of the foodborne disease burden epidemiology reference group (FERG). Appraising the evidence and reviewing the results**. 2008.
Reference Source

16. WHO: **WHO Initiative to Estimate the Global Burden of Foodborne Diseases. Fourth formal meeting of the Foodborne Disease Burden Epidemiology Reference Group (FERG)**. 2010.
Reference Source

17. WHO: **WHO initiative to estimate the global burden of foodborne diseases. Fifth formal meeting of the foodborne disease burden epidemiology reference group (FERG)**. 2013.
Reference Source

18. WHO: **Metrics: Disability-adjusted life year (DALY). Quantifying the burden of disease from mortality and morbidity**. Health Statistics and Information Systems, 2015.
Reference Source

19. Devleesschouwer B, Haagsma JA, Angulo FJ, *et al.*: **Methodological framework for World Health Organization estimates of the global burden of foodborne disease**. Submitted. 2015.

20. Cardoso AP, Mirione E, Ernesto M, *et al.*: **Processing of cassava roots to remove cyanogens.** *J Food Compost Anal.* 2005; **18**(5): 451–460.
Publisher Full Text

21. Cliff J: **Incidence and prevalence estimates of cassava cyanide-induced diseases**. WHO/FERG report. 2011; **75**.

22. Cliff J, Muquingue H, Nhassico D, *et al.*: **Konzo and continuing cyanide intoxication from cassava in Mozambique.** *Food Chem Toxicol.* 2011; **49**(3): 631–635.
PubMed Abstract | Publisher Full Text

23. Howlett WP, Brubaker GR, Mlingi N, *et al.*: **Konzo, an epidemic upper motor neuron disease studied in Tanzania.** *Brain.* 1990; **113**(Pt 1): 223–35.
PubMed Abstract | Publisher Full Text

24. WHO: **Weekly epidemiological record**. World Health Organization. 1996; **71**(30): 225–232.
Reference Source

25. Tylleskar T: **The causation of konzo: Studies on a paralytic disease in Africa**. Department of Pediatrics, International Child Health Unit, Uppsala University and Department of Epidemiology and Public Health. Umea University, 1994; **108**.
Reference Source

26. Bettencourt Mateus MS, Paquisse MM, Zangulo A, *et al.*: **Tropical spastic paraparesis; a major neurologic problem in Caungulia Angola related to of cassava: first report from Angola**. XXth World College of Neurology. Marrakesh. 2011.

27. Tshala-Katumbay D: **On the Site of the Lesion in Konzo: Clinical and Neurophysiological Studies on a Non-Progressive Upper Motor Neuron Disorder**. Faculty of Medicine. Uppsala, University of Uppsala, 2001; 72.
Reference Source

28. Banea M, Bikangi N, Nahimana G, *et al.*: **High prevalence of Konzo associated with a food shortage crisis in the Bandundu region of Zaire.** *Ann Soc Belg Med Trop.* 1992; **72**(4): 295–309.
PubMed Abstract

29. Ministry of Health Mozambique: **Mantakassa: an epidemic of spastic paraparesis associated with chronic cyanide intoxication in a cassava staple area of Mozambique. 2. Nutritional factors and hydrocyanic acid content of cassava products. Ministry of Health, Mozambique.** *Bull World Health Organ.* 1984; **62**(3): 485–92.
PubMed Abstract | Free Full Text

30. Tylleskär T, Banea M, Bikangi N, *et al.*: **Epidemiological evidence from Zaire for a dietary etiology of konzo, an upper motor neuron disease.** *Bull World Health Organ.* 1991; **69**(5): 581–589.
PubMed Abstract | Free Full Text

31. Salomon JA, Vos T, Hogan DR, *et al.*: **Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010.** *Lancet.* 2012; **380**(9859): 2129–2143.
PubMed Abstract | Publisher Full Text

32. Tylleskär T, Légué FD, Peterson S, *et al.*: **Konzo in the Central African Republic.** *Neurology.* 1994; **44**(5): 959–961.
PubMed Abstract | Publisher Full Text

33. Bonmarin I, Nunga M, Perea WA: **Konzo outbreak, in the south-west of the Democratic Republic of Congo, 1996.** *J Trop Pediatr.* 2002; **48**(4): 234–238.
PubMed Abstract | Publisher Full Text

34. Diasolua Ngudi D: **Konzo and cassava toxicity: a study of associated nutritional factors in the Popokabaka District, Democratic Republic of Congo**. Doctoral dissertation, Ghent University, 2005; 162.
Reference Source

35. Casadei E, Cliff J, Jansen P, *et al.*: **"Mantakassa" uma epidemia de neuropatia tropical associada com intoxicação por mandioca na Província de Nampula, Moçambique.** *Revista Médica de Moçambique.* 1984; **2**(1): 1–34.
Reference Source

36. Cliff J, Nicala D, Saute F, *et al.*: **Konzo associated with war in Mozambique.** *Trop Med Int Health.* 1997; **2**(11): 1068–1074.
PubMed Abstract | Publisher Full Text

37. Howlett W, Brubaker G, Mlingi N, *et al.*: **A geographical cluster of konzo in Tanzania.** *J of Tropical and Geographical Neurology.* 1992; **2**: 102–108.
Reference Source

38. Ezendam J, Loveren HV: **Parameters needed to estimate the global burden of peanut allergy: systematic literature review.** *Eur J of Food Res Rev.* 2012; **2**(2): 46–48.
Reference Source

39. Mullins RJ, Dear KB, Tang ML: **Characteristics of childhood peanut allergy in the Australian Capital Territory, 1995 to 2007.** *J Allergy Clin Immunol.* 2009; **123**(3): 689–693.
PubMed Abstract | Publisher Full Text

40. Flokstra-de Blok BM, Van der Velde JL, Vlieg-Boerstra BJ, *et al.*: **Health-related quality of life of food allergic patients measured with generic and disease-specific questionnaires.** *Allergy.* 2010; **65**(8): 1031–1038.
PubMed Abstract | Publisher Full Text

41. Hourihane JO, Roberts SA, Warner JO: **Resolution of peanut allergy: case-control study.** *BMJ.* 1998; **316**(7140): 1271–1275.
PubMed Abstract | Publisher Full Text | Free Full Text

42. Skolnick HS, Conover-Walker MK, Koerner CB, *et al.*: **The natural history of peanut allergy.** *J Allergy Clin Immunol.* 2001; **107**(2): 367–374.
PubMed Abstract | Publisher Full Text

43. Sicherer SH, Furlong TJ, Munoz-Furlong A, *et al.*: **A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants.** *J Allergy Clin Immunol.* 2001; **108**(1): 128–132.
PubMed Abstract | Publisher Full Text

44. Green TD, LaBelle VS, Steele PH, *et al.*: **Clinical characteristics of peanut-allergic children: recent changes.** *Pediatrics.* 2007; **120**(6): 1304–1310.
PubMed Abstract | Publisher Full Text

45. Moneret-Vautrin DA, Rancé F, Kanny G, *et al.*: **Food allergy to peanuts in France--evaluation of 142 observations.** *Clin Exp Allergy.* 1998; **28**(9): 1113–1119.
PubMed Abstract | Publisher Full Text

46. Liu Y, Wu F: **Global burden of aflatoxin-induced hepatocellular carcinoma: a risk assessment.** *Environ Health Perspect.* 2010; **118**(6): 818–824.
PubMed Abstract | Publisher Full Text | Free Full Text

47. JECFA (Joint FAO/WHO Expert Committee on Food Additives): **Aflatoxins. Safety Evaluation of Certain Food Additives and Contaminants.** World Health Organization, 1998.
Reference Source

48. WHO: **International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012**.
Reference Source

49. WHO: **Health Statistics and Information Systems**. Estimates for 2000–2012: Estimated deaths by cause, sex and WHO Member State, 2010; Estimated YLDs by cause, sex and WHO Member State, 2010; and Estimated YLLs by cause, sex and WHO Member State, 2010.
Reference Source

50. McDonald SA, Devleesschauwer B, Speybroeck N, *et al.*: **Data-driven methods for imputing national-level incidence in global burden of disease studies.** *Bull World Health Organ.* 2015; **93**(4): 228–236.
PubMed Abstract | Publisher Full Text | Free Full Text

51. Kensler TW, Qian GS, Chen JG, *et al.*: **Translational strategies for cancer prevention in liver.** *Nat Rev Cancer.* 2003; **3**(5): 321–329.
PubMed Abstract | Publisher Full Text

52. WHO: **Dioxins and their effects on human health: Fact Sheet No 225**. 2014.
Reference Source

53. Van Leeuwen FXR, Younes MM: **Consultation on assessment of the health risk of dioxins: re-evaluation of the tolerable daily intake (TDI): Executive summary.**

Food Addit Contam. 2000; **17**(4): 223–240.
PubMed Abstract | Publisher Full Text

54. Scientific Commission on Food: **Opinion of the Scientific Committee on Food on the Risk Assessment of Dioxins and Dioxin-like PCBs in Food.** SCF/CS/CNTM/DIOXIN/8 Final, 2000.
Reference Source

55. Scientific Commission on Food: **Opinion of the Scientific Committee on Food on the Risk Assessment of Dioxins and Dioxin-like PCBs in Food; Update based on new scientific information available since the adoption of the SCF opinion of the 22nd November 2000.** CS/CNTM/Dioxin/20 Final, 2001.
Reference Source

56. JECFA: **Joint FAO/WHO Expert Committee on Food Additives (JECFA), Safety evaluation of certain food additives and contaminants.** WHO Food Additives Series 48, 2002.
Reference Source

57. JECFA: **Joint FAO/WHO Expert Committee on Food Additives (JECFA), Summary and Conclusions of the sixty-fourth meeting**. 2005.
Reference Source

58. US EPA: **Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments**. 2012; **1**. (CAS No. 1746-01-6), EPA/600/R-10/038F.
Reference Source

59. Patterson DG Jr, Needham LL, Pirkle JL, *et al.*: **Correlation between serum and adipose tissue levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in 50 persons from Missouri.** *Arch Environ Contam Toxicol.* 1988; **17**(2): 139–143.
PubMed Abstract | Publisher Full Text

60. LaKind JS, Berlin CM Jr, Sjödin A, *et al.*: **Do human milk concentrations of persistent organic chemicals really decline during lactation? Chemical concentrations during lactation and milk/serum partitioning.** *Environ Health Perspect.* 2009; **117**(10): 1625–1631.
PubMed Abstract | Publisher Full Text | Free Full Text

61. Nakamura T, Nakai K, Matsumura T, *et al.*: **Determination of dioxins and polychlorinated biphenyls in breast milk, maternal blood and cord blood from residents of Tohoku, Japan.** *Sci Total Environ.* 2008; **394**(1): 39–51.
PubMed Abstract | Publisher Full Text

62. Wittsiepe J, Fürst P, Schrey P, *et al.*: **PCDD/F and dioxin-like PCB in human blood and milk from German mothers.** *Chemosphere.* 2007; **67**(9): S286–294.
PubMed Abstract | Publisher Full Text

63. Conference of the Parties to the Stockholm Convention on Persistent Organic Pollutants, Sixth meeting. United Nations Environmental Programme (UNEP): **Human exposure to POPs across the globe: POPs levels and human health implication: Results of the WHO/UNEP human milk survey**. 2013. Geneva, Switzerland.
Reference Source

64. Van der Voet H, Slob W: **Integration of probabilistic exposure assessment and probabilistic hazard characterization.** *Risk Anal.* 2007; **27**(2): 351–371.
PubMed Abstract | Publisher Full Text

65. Slob W, Bakker MI, Biesebeek JD, *et al.*: **Exploring the uncertainties in cancer risk assessment using the integrated probabilistic risk assessment (IPRA) approach.** *Risk Anal.* 2014; **34**(8): 1401–1422.
PubMed Abstract | Publisher Full Text

66. Crump KS: **A new method for determining allowable daily intakes.** *Fundam Appl Toxicol.* 1984; **4**(5): 854–871.
PubMed Abstract | Publisher Full Text

67. European Food Safety Authority: **Use of the benchmark dose approach in risk assessment. Guidance of the Scientific Committee (Question No. EFSA-Q-2005-232)**. *EFSA J.* 2009; **1150**: 1–72.
Publisher Full Text

68. Slob W: **Dose-response modeling of continuous endpoints.** *Toxicol Sci.* 2002; **66**(2): 298–312.
PubMed Abstract | Publisher Full Text

69. Zeilmaker MJ, DeVleesschauwer B, Mengelers MJB, *et al.*: **The disease burden of dioxins: A global perspective (manuscript in preparation)**.

70. Baccarelli A, Giacomini SM, Corbetta C, *et al.*: **Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin.** *PLoS Med.* 2008; **5**(7): e161.
PubMed Abstract | Publisher Full Text | Free Full Text

71. Aoki Y, Belin RM, Clickner R, *et al.*: **Serum TSH and Total T_4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002).** *Thyroid.* 2007; **17**(12): 1211–1223.
PubMed Abstract | Publisher Full Text

72. Gray LE, Ostby JS, Kelce WR: **A dose-response analysis of the reproductive effects of a single gestational dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in male Long Evans Hooded rat offspring.** *Toxicol Appl Pharmacol.* 1997; **146**(1): 11–20.
PubMed Abstract | Publisher Full Text

73. Cooper TG, Noonan E, Von Eckardstein S, *et al.*: **World Health Organization reference values for human semen characteristics.** *Hum Reprod Update.* 2010; **16**(3): 231–245.
PubMed Abstract | Publisher Full Text

74. National Toxicology Program (NTP): **Toxicology and Carcinogenesis Studies of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) (CAS No. 1746-01-6) in Female Harlan Sprague-Dawley Rats (Gavage Studies).** TR 521, Research Triangle Park, NC, USA. 2006.

75. National Toxicology Program (NTP): **Toxicology and Carcinogenesis Studies of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) (CAS No. 57117-31-4) in Female Harlan Sprague-Dawley Rats (Gavage Studies).** TR 525, Research Triangle Park, NC, USA. 2006.

76. Van den Berg M, Birnbaum LS, Denison M, *et al.*: **The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds.** *Toxicol Sci.* 2006; **93**(2): 223–241.
PubMed Abstract | Publisher Full Text | Free Full Text

77. WHO: **Global burden of disease regions used for WHO-CHOICE analyses. Cost effectiveness and strategic planning**. 2015.
Reference Source

78. Wild CP, Hall AJ: **Primary prevention of hepatocellular carcinoma in developing countries.** *Mutat Res.* 2000; **462**(2–3): 381–393.
PubMed Abstract | Publisher Full Text

79. Gibb H, Devleesschauwer B, Bolger PM, *et al.*: **Dataset 1 in: World Health Organization estimates of the global and regional disease burden of four foodborne chemical toxins, 2010.** *F1000Research.* 2015.
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Gibb *et al*. have made an important contribution to our understanding of the population health impacts of food-borne chemical exposures. I noted one minor data gap in the description of the approach taken for the dioxin analysis. In contrast to the other chemicals assessed, the authors did not report the disability weights (DWs) for dioxin outcomes in the main text; they are found only in the Supplementary material.

My main questions, however, relate to the conclusions. I feel that two of the paper's bottom lines (on raising awareness of the impacts of food-borne chemicals and the need for better exposure data) deserve additional attention.

On raising awareness: after reading the article, I was looking for some further characterization of the burden estimates. The estimates do seem substantial but what is the appropriate context for reference? The authors make reference to a Dutch National Institute for Public Health and the Environment assessment that made some comparisons of disease burdens for both chemicals and infectious agents in foods (listed as reference #12 Van Kreijl et al 2006). Perhaps that approach or some comparisons of the reported burden estimates to the total burden of the outcomes assessed could be made. Some further characterization of the burden estimates would assist the effort to raise awareness in the public health community.

On better exposure data: The main text of the paper focuses largely on the outcomes or health effects related to the chemicals. Little is said about the exposure beyond an understanding that most exposures come from food. Description of the types of exposure data represented in the literature underlying the analysis would better set up the call for biomonitoring at the conclusion.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 25 January 2016

doi:10.5256/f1000research.7910.r12086

George M. Gray
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This paper is a very useful addition to the goal of characterizing the disease burden from food contaminants. It applies appropriate, and for some contaminants state-of-the-art, analytic approaches. The fact that virtually all exposure to the four contaminants evaluated comes from food illustrates the importance of the exercise.

There are a few issues that deserve attention:

- It is difficult to tell from the manuscript whether the dose-response information for dioxins is from the epidemiologic study cited or from the animal studies. It is unfortunate that further information on the dose response refers to a manuscript in preparation and thus unavailable.

- What is the appropriate weighting for a substance that causes infertility? Presumably some number of affected individuals would want to reproduce and the exposure is effectively causing an entire lifetime of YLL for the child not born.

- I appreciate very much the effort to consider uncertainty in the projections from this analysis. However, it is very important not to imply greater characterization of uncertainty than has occurred. In this analysis the uncertainty bounds presented are primarily based on ranges for specific parameters in the models used to estimate YLL and YLD. Model uncertainty, for example, is not considered. Insofar as dose-response data for dioxins were generated from animal data (see point above) there is considerable quantitative uncertainty introduced by using animals as a model for humans. Similarly, in the case of aflatoxin it is recognized that a “bottom up” rather than “top down” model of analysis yields very different estimates of risk and uncertainty and it is not clear which is the better approach. Statements like that in paragraph 2 of the results section “The DALY estimates for aflatoxin and dioxin have the least uncertainty..” are likely to be misinterpreted. The smallest calculated uncertainty is not the same as the smallest range of actual uncertainty if all sources have not been considered.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 05 January 2016

doi:10.5256/f1000research.7910.r11682

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For the estimate of Konzo , it was multiple by 10. I would suggest a range as it is an estimate based on poor reporting. Is there another disease to model off to get a better range?

The rest of the article is acceptable.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Author Response 26 Jan 2016

Herman Gibb, Gibb Epidemiology Consulting LLC, USA

In the section on cyanide in cassava, a range of 1 to 10-fold was reported: "It was therefore decided to account for the uncertainty in the underreporting by applying an expansion factor ranging uniformly from 1 to 10 to the observed cases."

Competing Interests: There are no competing interests.